SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 16 to correct a typographical error. Support for amended Claim 16 can be found in the same claim, as previously presented.

No new matter has been added. Claims 16, 17 and 34-48 are active in this application.

Applicants note that, in the Advisory Action, the Examiner indicated that the amendments to the claims filed on April 29, 2008, would be entered for purposes of Appeal. However, since Applicants are not proceeding to appeal, the amendments to the claims are not entered. Accordingly, the Amendments to the Claims beginning on page 2 of this response are provided relative to the last entered amendment filed on November 30, 2007.

REMARKS

At the outset, Applicants' representative wishes to thank Examiner Alstrum Acevedo for withdrawing the rejections based on U.S. Patent No. 5,653,961 (McNally et al.).

Present Claims 16, 17, and 34-48 relate to aerosols,

which are produced from a solution consisting of:

one or more solubilized active material(s),

a propellant consisting of a mixture of HFA 227 and HFA 134a, and ethanol as a cosolvent;

wherein the ratio of HFA 227:HFA 134a ranges from 10:90 to 90:10;

wherein said aerosol is composed of particles which have a mass median aerodynamic diameter greater than 2 μm,

wherein at least 40% of said aerosol is composed of fine particles having a diameter of less than 4.7μm, and

wherein said one or more active materials is at least one member selected from the group consisting of salbutamol, salts of salbutamol, beclometasone dipropionate, ipratropium bromide, and combinations thereof.

An object of the present invention is to modulate the MMAD of a solution aerosol formation based on HFAs propellants, in particular HFA 134a and HFA 227, in order to obtain compositions suitable for pulmonary administration, having size characteristics similar to those of compositions based on CFCs, so as to avoid systemic absorption of the active material. This object is achieved by means of the aerosol according to present Claim 1, i.e., an aerosol characterized by having an MMAD greater than 2 μm and an amount of at least 40% of fine particles having a diameter of less than 4.7 μm. It has in fact been found that, in aerosol formulations based on mixtures of HFA 134a and HFA 227, the MMAD must be greater than 2 μm in order to avoid side effects due to systemic absorption and that both parameters are critical for the solution of the technical problem. Notably, neither of factors is taught or even suggested by the prior art.

The inventors have discovered that the presently claimed aerosols are particularly effective for delivering substances to the respiratory tract. The cited references neither disclose nor suggest the presently claimed aerosols or the benefits provided thereby. Accordingly, this reference cannot affect the patentability of the present claims.

The rejection of Claims 16, 17, 35, 37, 39, 41, 43, 45, and 47 under 35 U.S.C. 103(a) in view of U.S. Patent No. 5,776,432 (Schultz et al.) and the rejection of Claims 34, 36, 38, 40, 42, 46, and 48 under 35 U.S.C. 103(a) in view of Schultz et al. and further in view of U.S. Patent No. 6,126,919 (Stefely et al.) are respectfully traversed.

Schultz et al. discloses certain aerosol formulations. On page 5 of the Office Action the position is taken that the formulation of this reference would inherently deliver an aerosol

composed of particles which have the claimed mass median aerodynamic diameter. However, this assertion is incorrect.

In fact, Schultz et al. corresponds to EP 0 553 298, which is discussed on page 7, line 25, to page 8, line 22, of the specification. As explained on page 8 of the present specification, formulations like those of Schultz et al. deliver particles having a particle size distribution with a MMAD of 1.1 μm. This assertion is supported by C. Leach, "Enhanced Drug Delievery through Reformulating MDIs with HFA Propellants-Drug Deposition and its Effect on Preclinical and Clinical Programs," in Respiratory Drug Delivery V, pp. 133-144 (1996) (Leach, copy attached hereto as Exhibit A). In particular, the Examiner's attention is directed toward page 138 of Leach, where it is disclosed that the

> new HFA-134a-beclomethasone dipropionate (HFA-BDP) formulation is a solution which delivers a particle size MMAD of 1.1 microns (measured by Anderson impactor) . . .

See, Leach, at 138.

In contrast, as noted above, the present claims require the aerosol to be composed of particles which have a mass median aerodynamic diameter greater than 2 μm.

As explained in the present specification:

> a particle size distribution with a MMAD of 1.1 μm [...] means that the peripheral pulmonary deposition of very small particles increases and submicronic particles can easily be directly absorbed from the alveoli into the bloodstream. The rate and ***extent of systemic absorption is significantly increased*** and as a consequence undesired effects, for example certain side effects, can increase. A relatively large fraction of the dose is exhaled.

See, page 8, lines 12-18.

There is no teaching in Schultz et al. of a formulation which delivers an aerosol composed of particles which have a mass median aerodynamic diameter greater than 2 μm. Moreover, there is no teaching in this reference which would suggest any advantage to be gained from such a formulation. Simply put, Schultz et al. does not suggest modulating the

MMAD and the diameter of the fine particles, nor does this reference give any hint or suggestion to do so in order to obtain an aerosol formulation with no systemic adsorption.

Accordingly, this reference cannot make the present claims obvious.

Applicants respectfully submit that there is nothing in Stefely et al. which can cure this basic deficiency of Schultz et al. Stefely teaches the use of specific biocompatible polymers dissolved in medicinal formulations in order to help solubilize and/or chemically stabilize a drug, so as to provide sustained release of that drug. Thus, this reference is concerned with a completely different technical problem and offers a different solution, without giving any hint or suggestion to modify the MMAD and the diameter of the fine particles so as to arrive at the presently claimed formulations.

Therefore, a skilled person would not have been motivated to combine Schultz et al. and Stefely et al. Further, even if one of skill in the art did combine the teachings of these references, he/she would not arrive at the presently claimed aerosols.

In the Advisory Action, the position is taken that aerosol formulations must have a MMAD of 10 microns or less and that such a range overlaps with the claimed value of greater than 2. However, as noted above, Leach discloses that formulations such as disclosed in Schultz et al. have a MMAD of 1.1 microns (*see*, Leach, at 138). Notably, 1.1 microns is also less than 10 microns. Accordingly, the fact that the formulations of Schultz et al. have a MMAD of 1.1 microns is not inconsistent with the assertion that aerosol formulations must have a MMAD of 10 microns or less.

Simply put, the only evidence of record indicates that the formulations of Schultz et al. have a MMAD of 1.1 microns, not greater than 2 microns.

Moreover, even if one of skill in the art were motivated to increase the MMAD of the formulations of Schultz et al., there is nothing in the cited references which would suggest any method for doing so.

For these reasons, the rejections should be withdrawn.

The rejection of Claims 16, 17, and 34-48 under the judicially-created doctrine of obviousness-type double patenting in view of claims 1-12, 14 and 16-29 of U.S. Patent No. 6,713,047 in view of Stefely et al.; the rejection of Claims 34-48 under the judicially-created doctrine of obviousness-type double patenting in view of claims 1-4, 15, and 17 of U.S. Patent No. 6,716,414; and the rejection of Claims 34-48 under the judicially-created doctrine of obviousness-type double patenting in view of claims 1-6, 10, and 22-24 of U.S. Patent No. 6,964,759 in view of Stefely et al. are all respectfully traversed. Applicants respectfully submit that there is nothing in any of the claims of the cited patents which would suggest the presently claimed aerosols. Quite simply, none of the claims of any of the cited patents recite the presently claimed MMAD. Accordingly, the rejections should be withdrawn.

The rejection of Claims 16, 17, and 34-38 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 11, 14-16, 20, 21, 30-32, and 42-44 of U.S. Patent Application Serial No. 09/831,888 (now U.S. Patent No. 7,347,199) is respectfully traversed. Quite simply, none of the claims of this patent recite the presently claimed MMAD.

The provisional rejection of Claims 16 and 17 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 1, 4-7, and 13 of co-pending U.S. Patent Application Serial No. 10/505,679; the provisional rejection of Claims 34-38 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 24, 25, 33, and 37-41 of co-pending U.S. Patent Application Serial No. 10/435,032; and the provisional rejection of Claims 34-38 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 24, 30, 33, 34, 40, 45-49, and 52 of co-pending U.S. Patent Application Serial No. 10/435,354 are respectfully requested to be held in abeyance pending the identification of otherwise allowable subject matter.

Applicants respectfully submit that the present application is now in condition for allowance, and early notification to that effect is earnestly solicited.

Respectfully submitted,

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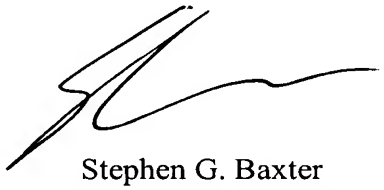

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